Sepsis ve miRNA: Yeni Nesil Biyobelirteçlere Doğru

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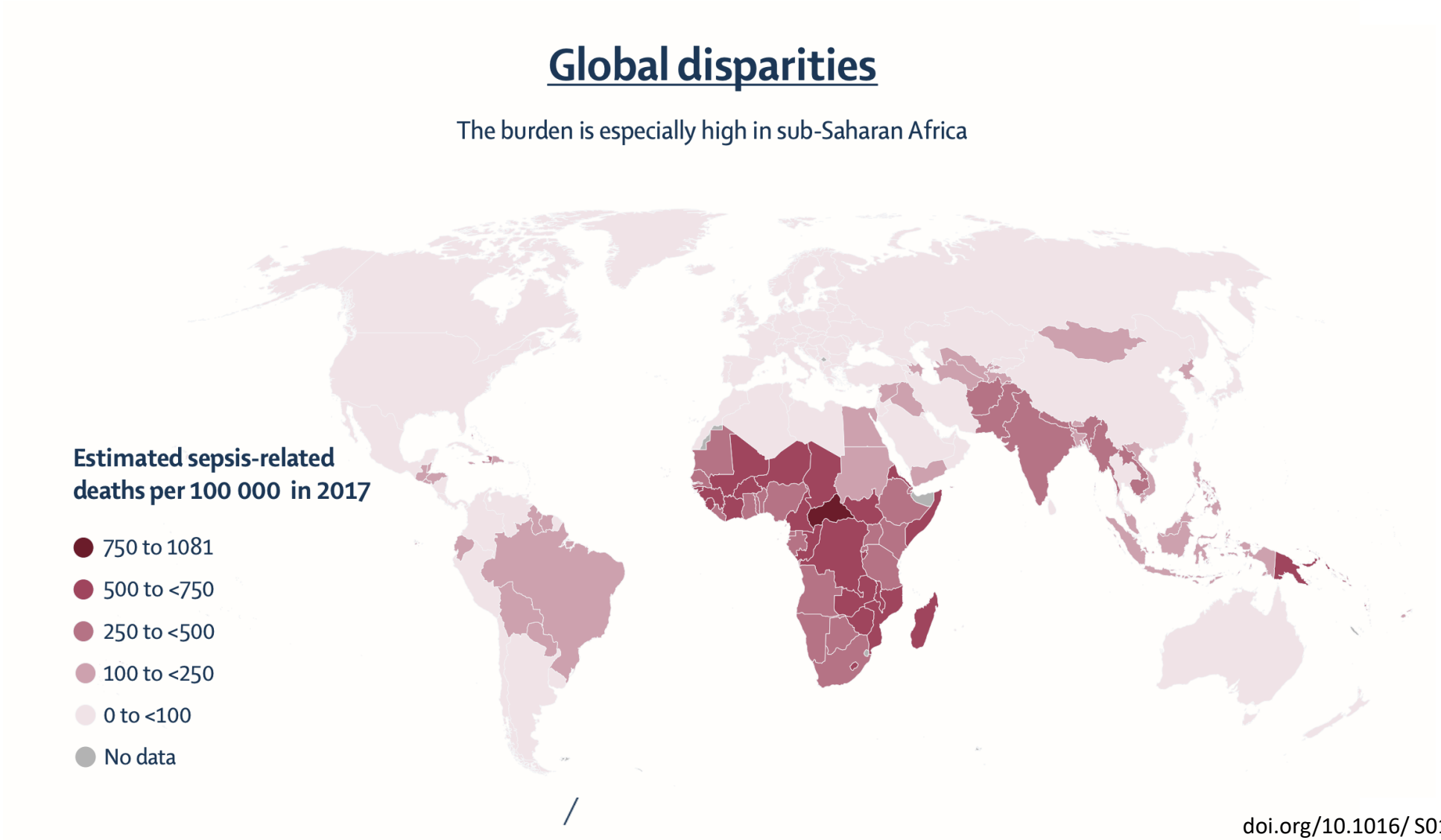
- Sepsis tedavisinde miRNA
- Sonuç

Vaka Tartışması

- 45 yaşında sağlıklı erkek hasta
- Ateş, halsizlik, titreme, konfuzyon
- Ateş: 39.2°C
- KB: 100/62 mmHg
- Nabız: 118 bpm
- SS: 24/min
- SpO_2: 94%

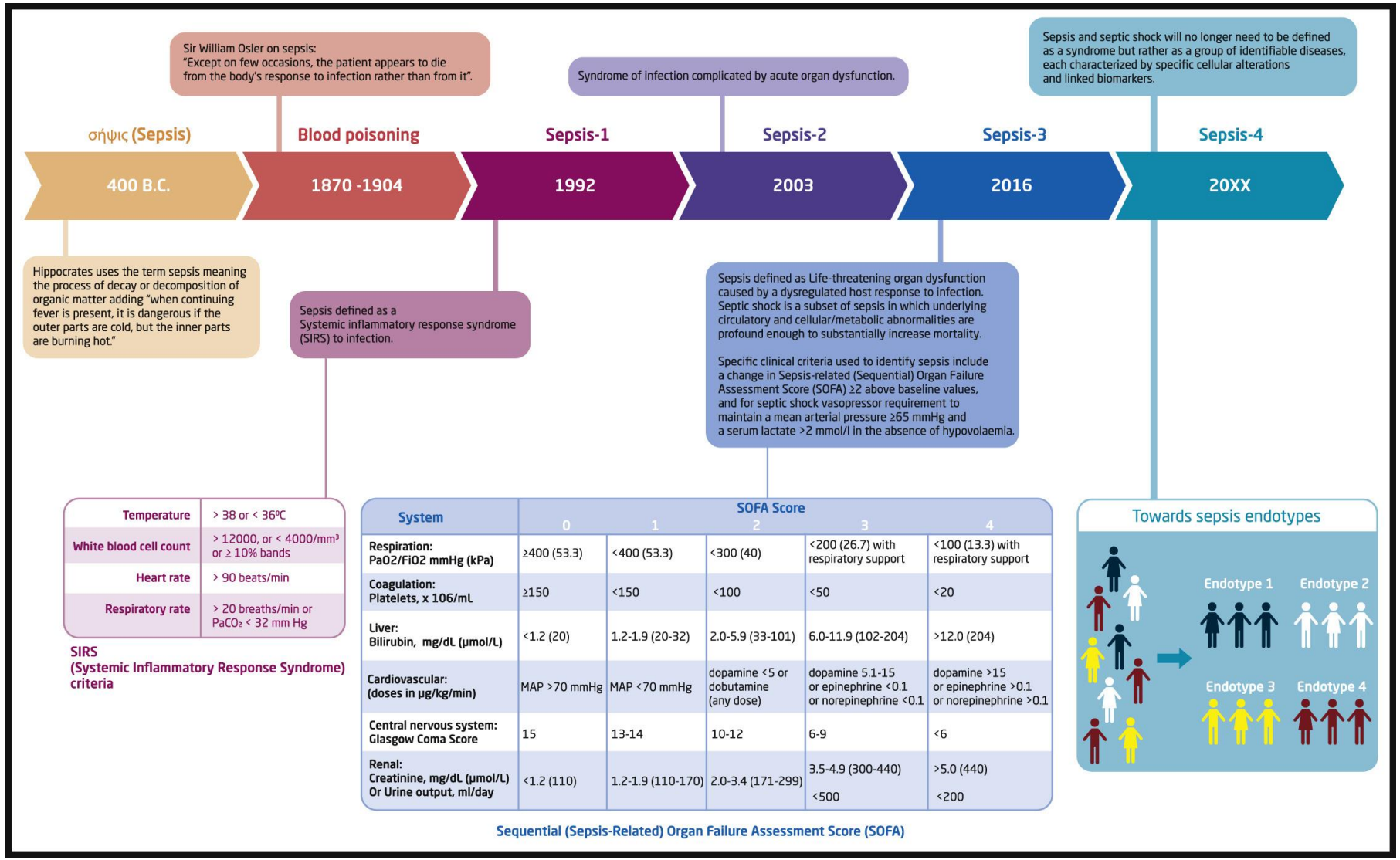
- Her iki akciğer bazal raller
- Konfuzyon
- Gecikmiş kapiller dolum
- SOFA : 9
- WBC: 16,200 /µL (nötrofil: % 88)
- CRP: 226 mg/L
- Laktat: 3.8 mmol/L
- Kreatinin: 1.9 mg/dL
- Bilirubin: 2.1 mg/dL
- INR: 1.6

Sepsis tanımı ve tarihçesi



doi.org/10.1016/ S0140-6736(19)32989-7

Sepsisin Zaman Yolculuğu



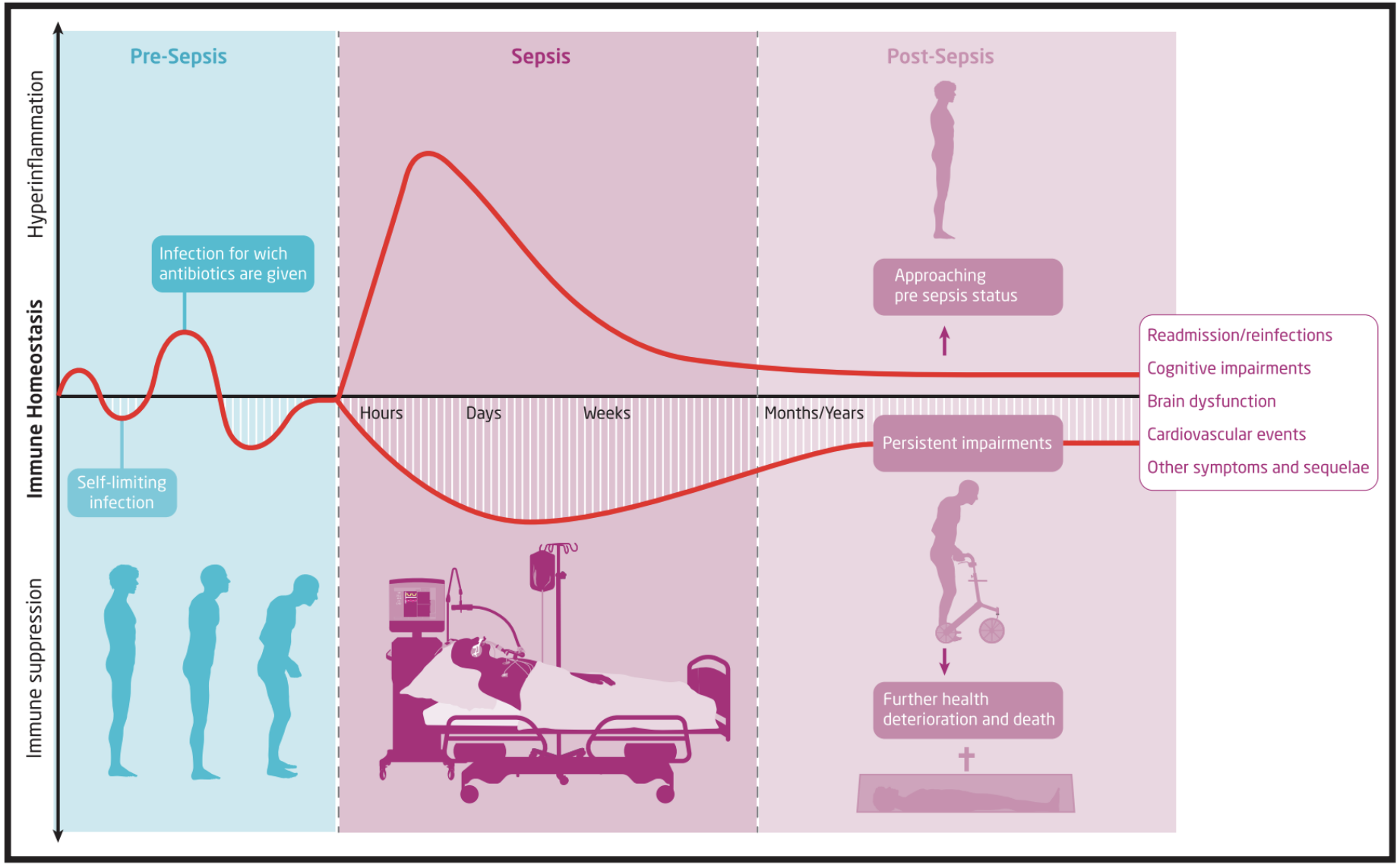
Temperature	> 38 or < 36ºC
White blood cell count	> 12000, or < 4000/mm³ or ≥ 10% bands
Heart rate	> 90 beats/min
Respiratory rate	> 20 breaths/min or $PaCO_2$ < 32 mm Hg

SIRS (Systemic Inflammatory Response Syndrome) criteria

System	SOFA Score 0	1	2	3	4
Respiration: PaO2/FiO2 mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation: Platelets, x 106/mL	≥150	<150	<100	<50	<20
Liver: Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular: (doses in µg/kg/min)	MAP >70 mmHg	MAP <70 mmHg	dopamine <5 or dobutamine (any dose)	dopamine 5.1-15 or epinephrine <0.1 or norepinephrine <0.1	dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system: Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal: Creatinine, mg/dL (µmol/L) Or Urine output, ml/day	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5.0 (440) <200

Sequential (Sepsis-Related) Organ Failure Assessment Score (SOFA)

Bir Bağışıklık Yolculuğu: Sepsis'in Ötesi



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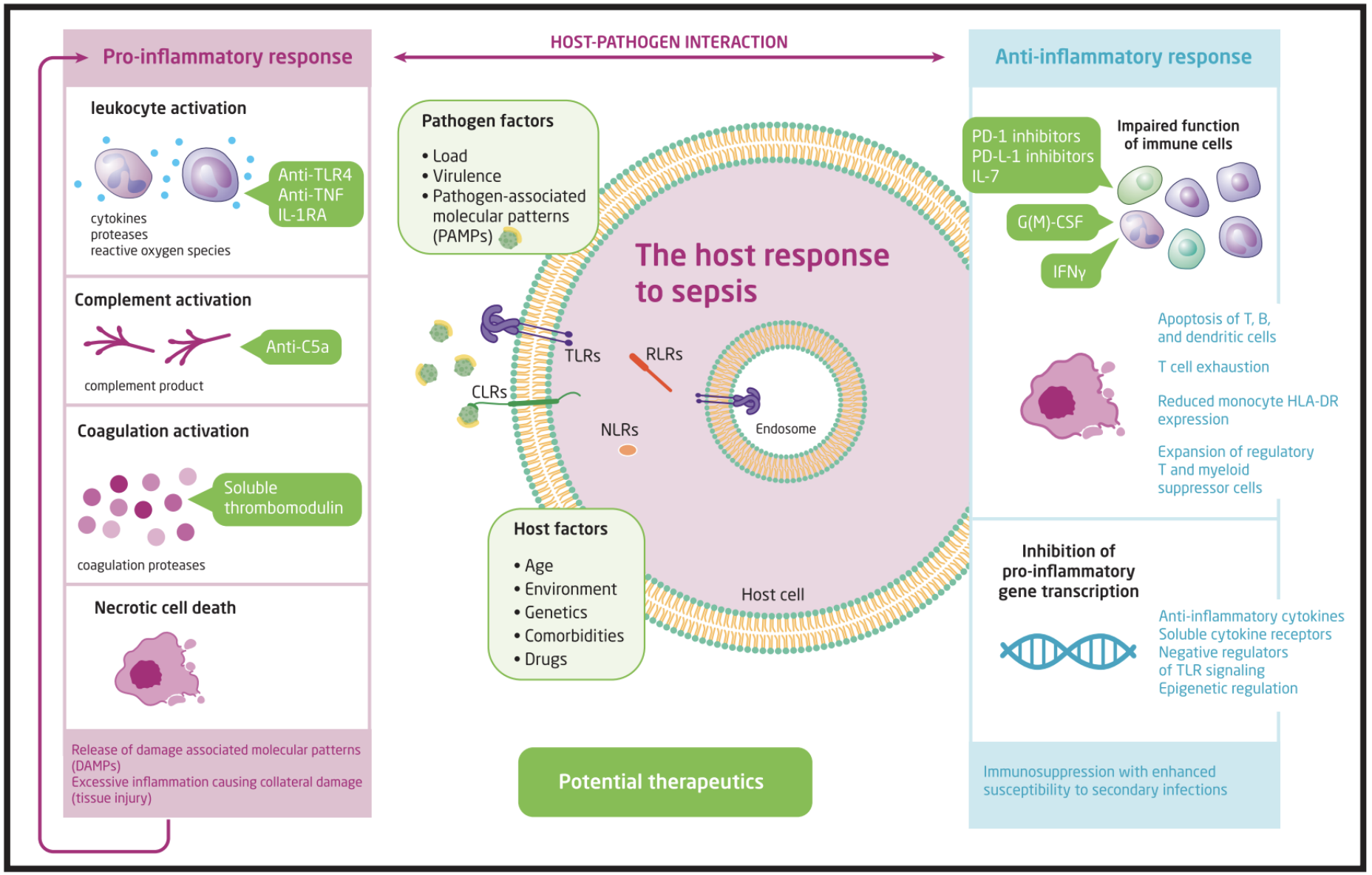
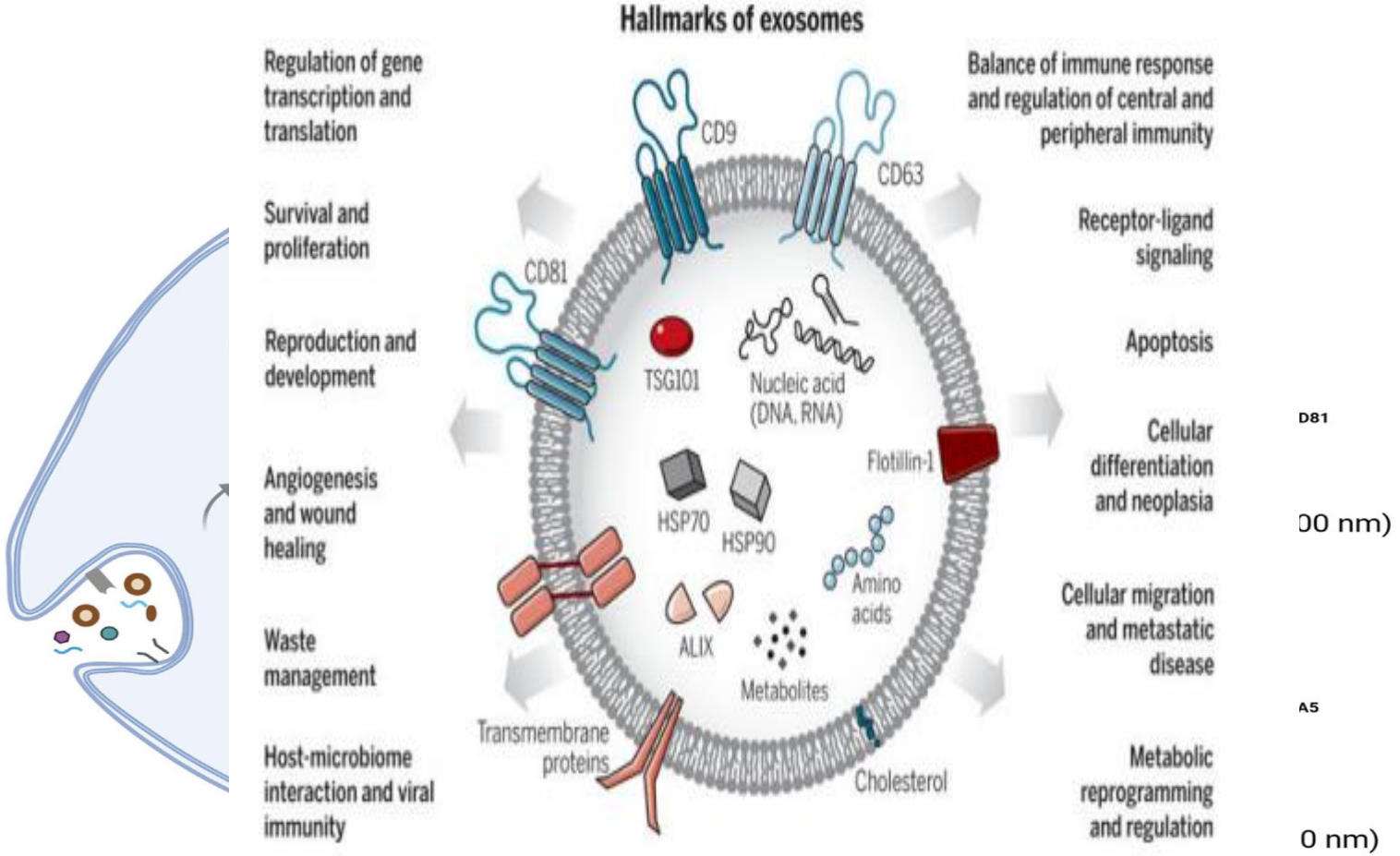


Sepsiste Sessiz Kurye: Eksozomlar ve Taşıdıkları miRNA Mesajları



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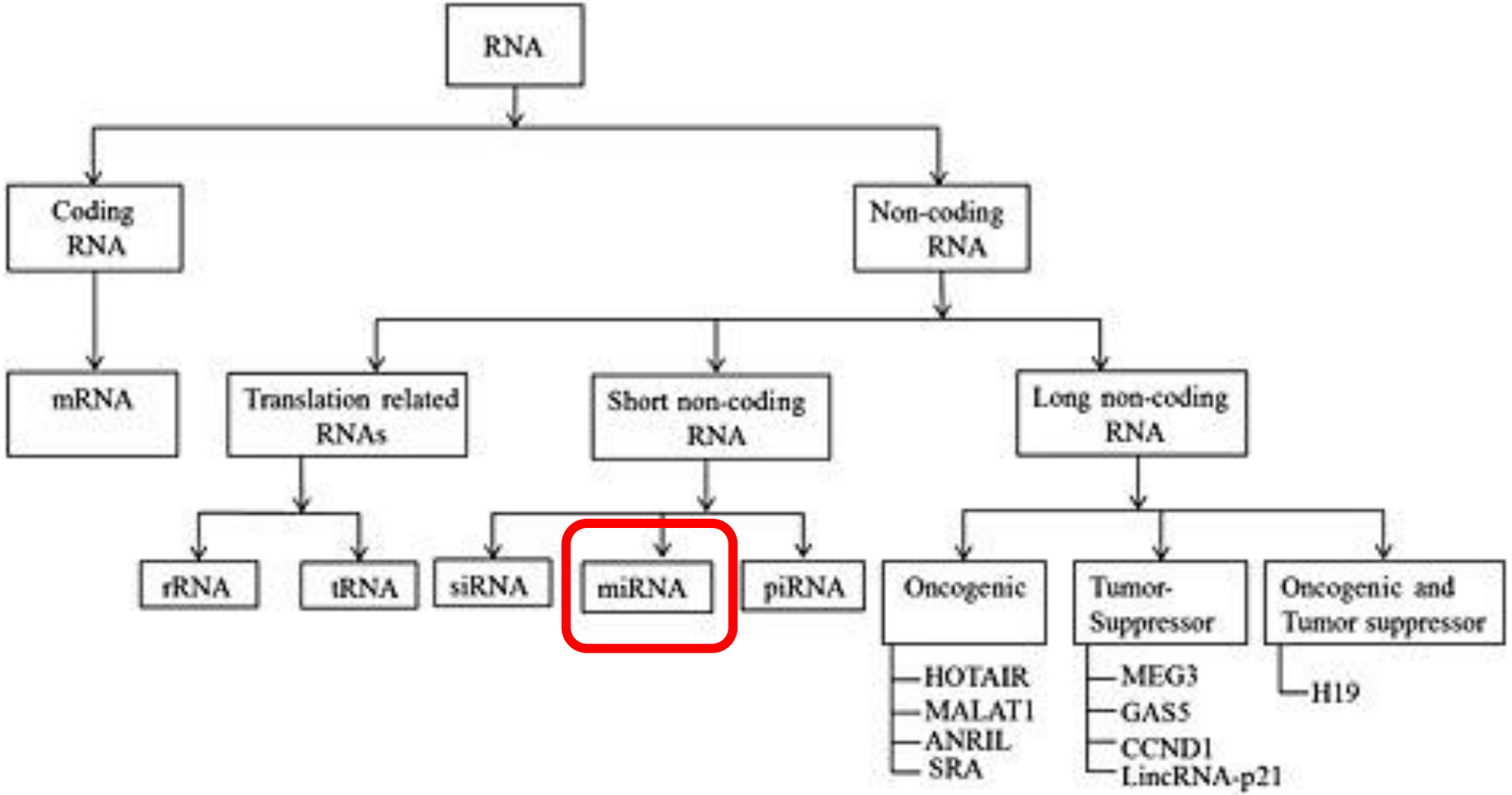

10.1002/cbf.3079

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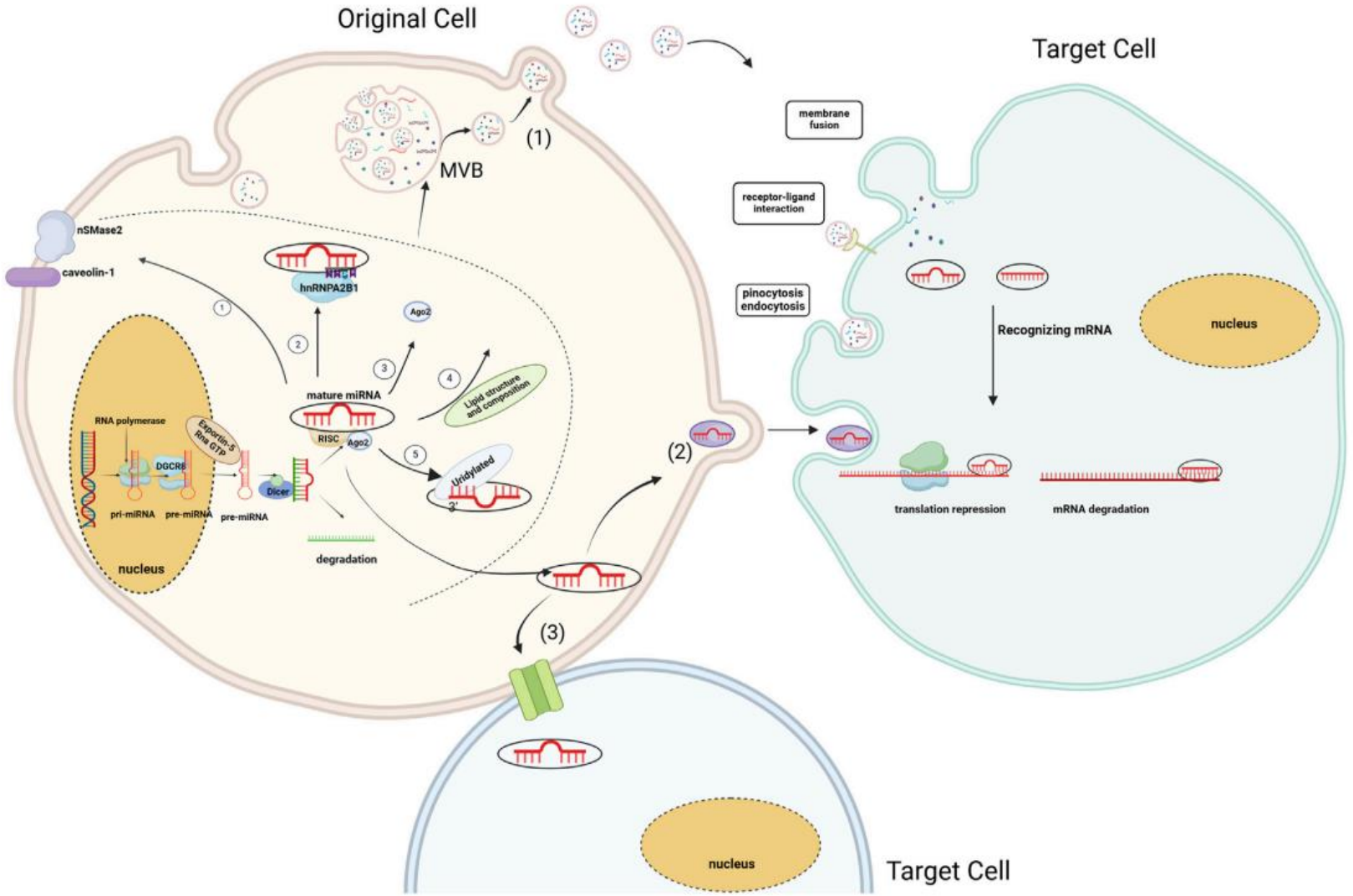

10.3389/fphar.2024.1452276

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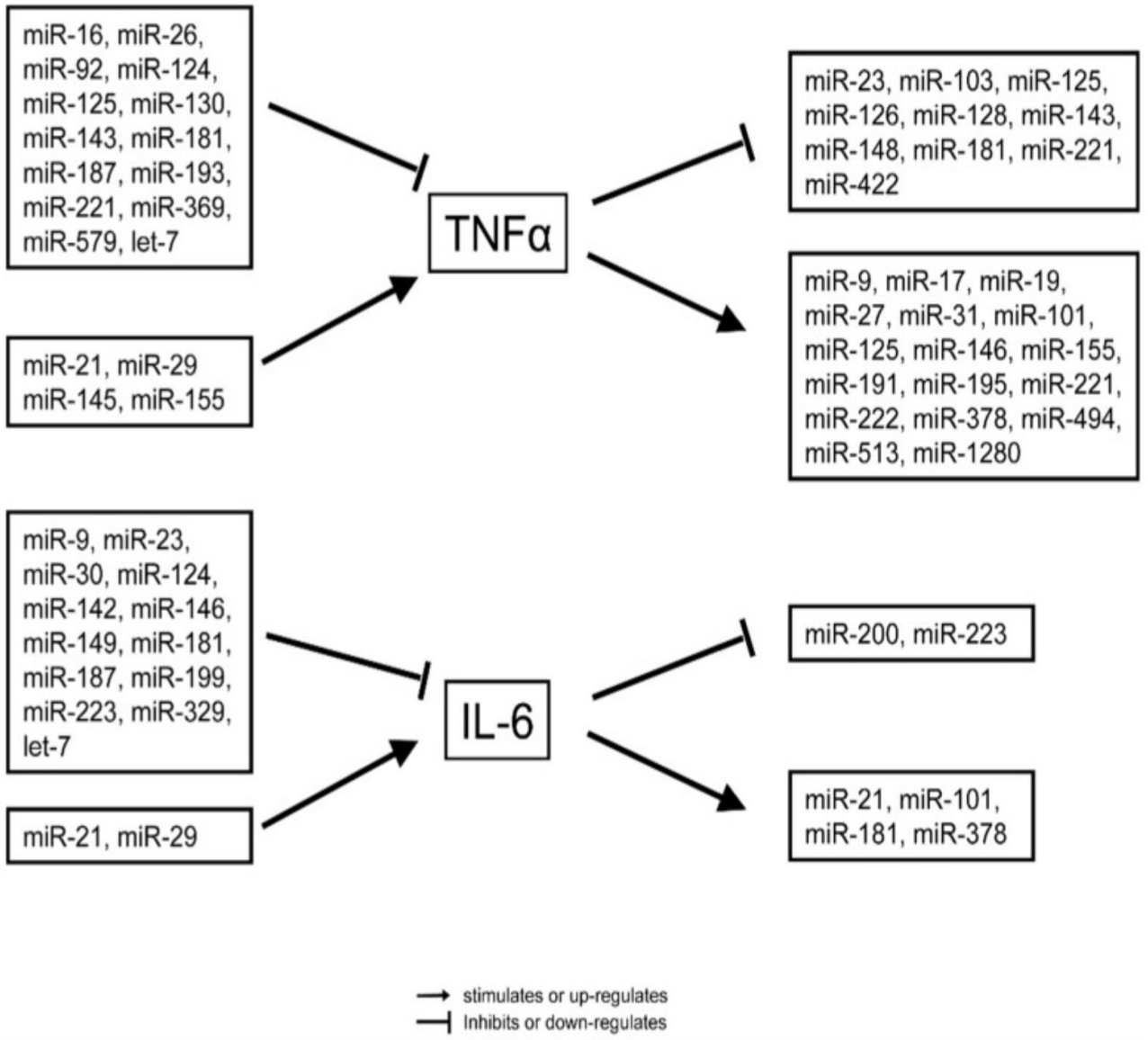
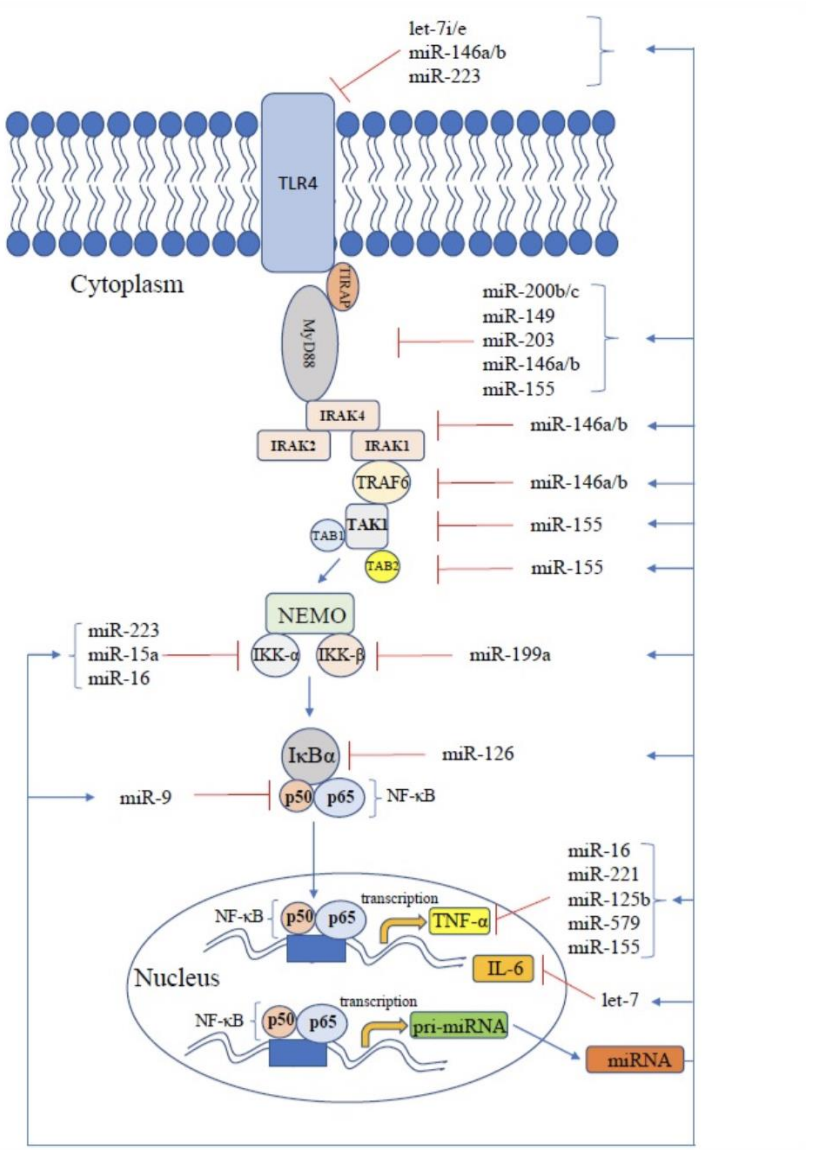




Sepsiste Sessiz Kurye: Eksozomlar ve Taşıdıkları miRNA Mesajları

Sepsiste miRNA

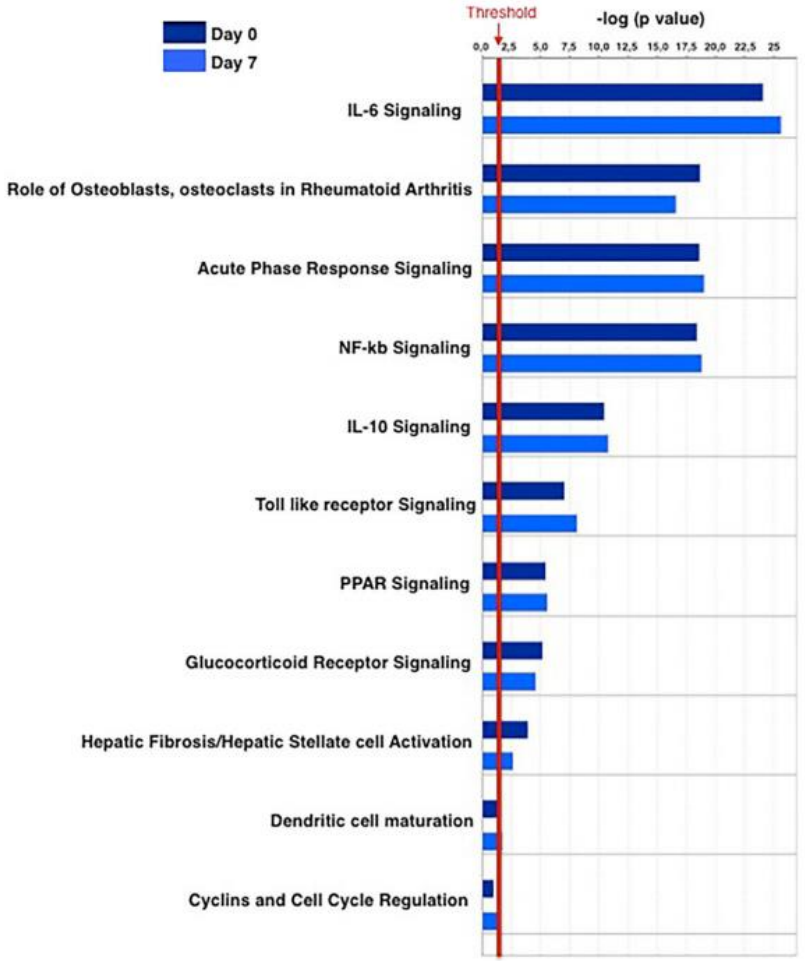
Real et al. Critical Care (2018) 22:68
https://doi.org/10.1186/s13054-018-2003-3

Critical Care

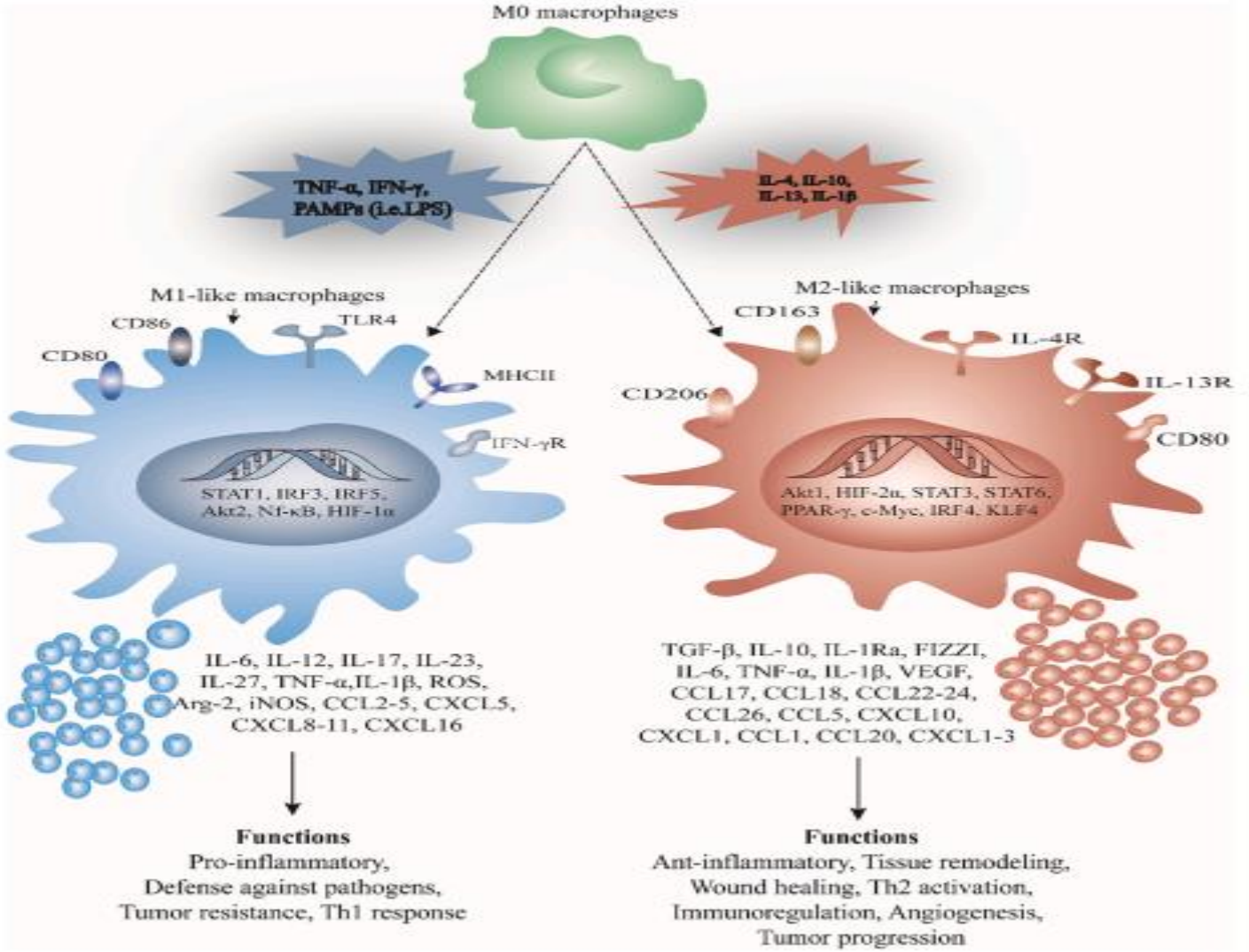
RESEARCH Open Access

Exosomes from patients with septic shock convey miRNAs related to inflammation and cell cycle regulation: new signaling pathways in sepsis?

Juliana Monte Real[1,2,3], Ludmila Rodrigues Pinto Ferreira[4,5], Gustavo Henrique Esteves[6],



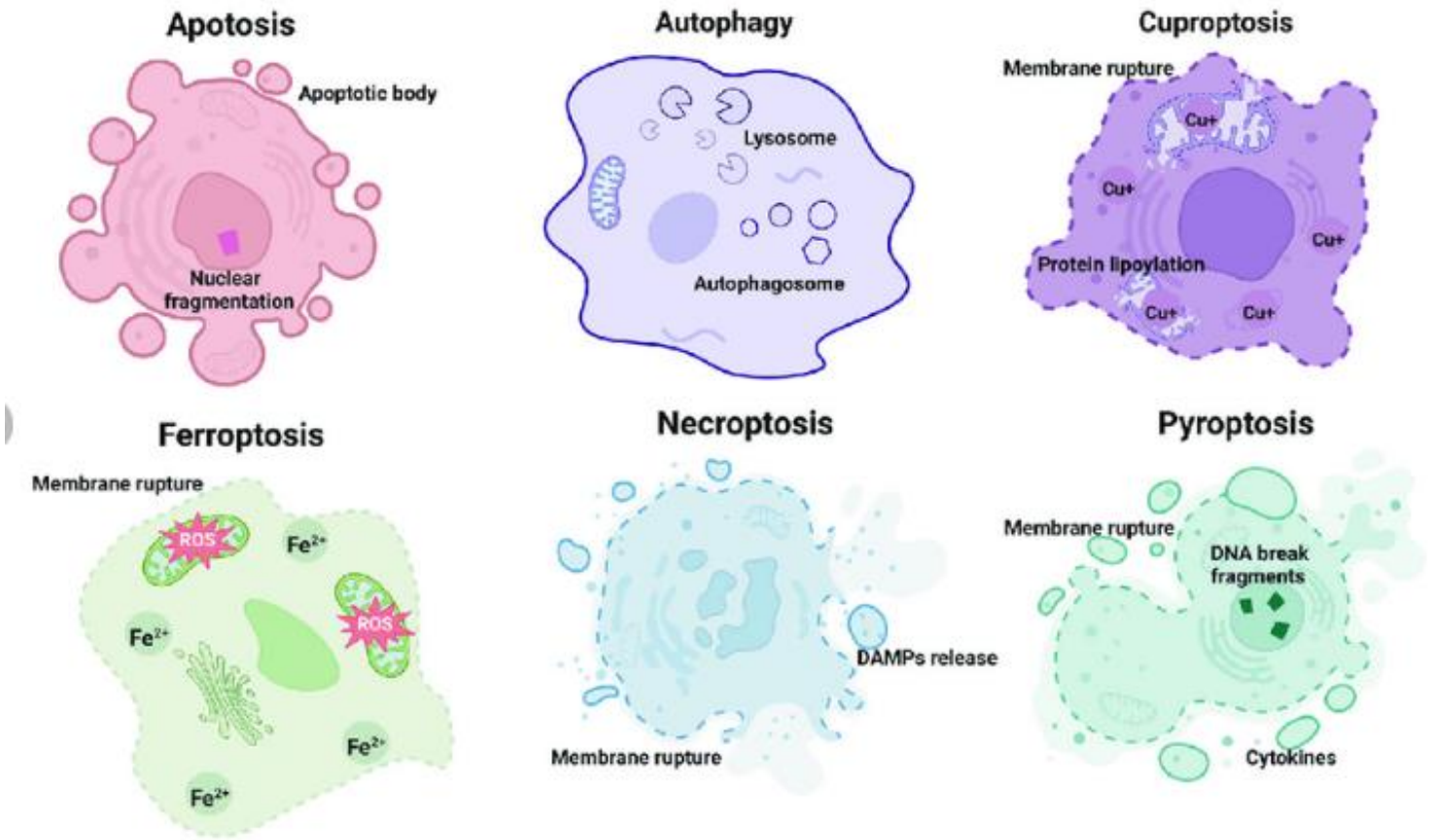
Makrofaj polarizasyonu



Makrofaj polarizasyonu

Pathological phenotype	miRNA	Regulation in sepsis	Sample source	Target cell	Potential functional mechanism	Ref.
Regulation of Immune Response	miR-155	Up	Serum	Macrophages	Targeting SHIP1 and SOCS1 to promote macrophage proliferation and inflammation	Jiang et al. (2019)
	miR-155-5p	Up	Stimulated macrophages	Macrophages	Downregulating of MSK1 expression and activating the p38/MAPK pathway	Xu et al. (2023)
	miR-30d-5p	Up	Polymorphonuclear neutrophils	Macrophages	Targeting SOCS-1 and SIRT1 and activating the NF-κB pathway	Jiao et al. (2021)
	miR-19b-3p	Up	Tubular epithelial cells	Macrophages	Targeting SOCS-1 and activating the NF-κB pathway	Lv et al. (2020)
	miR99a/b	Up	Endothelial cells	Monocyte	Altering the expression of monocyte surface CD11b and MHCII	Fitzpatrick et al. (2022)
	miR-1298-5p	Up	Serum	BEAS-2B	Targeting SOCS6 via STAT3 pathway to increased cell permeability and inflammatory response	Ma et al. (2021)

Programlı hücre ölümü



Programlı hücre ölümü

Pathological phenotype	miRNA	Regulation in sepsis	Sample source	Target cell	Potential functional mechanism	Ref.
Programmed Cell Death	hsa-miR-1262	Up	Serum	Myocardial cell	Silencing of SLC2A1 promoted apoptosis and suppressed glycolysis in cells	Sun et al. (2022a)
	miR-885-5p	Up	Serum	Myocardial cell	Targeting HMBOX1 and activating the NF-κB pathway	Tu et al. (2022)
	miR-93-5p	Up	Macrophages	Renal epithelial cells	Targeting TXNIP to mediate the pyroptosis of renal epithelial cells	Juan et al. (2021)
	miR-210-3p	Up	Plasma	BEAS-2B	Targeting ATG7 to inhibit the effect of ATG7 on autophagy, promoting cell apoptosis	Li et al. (2021)
	MiR-223-3p	Down	Plasma	Human coronary artery endothelial cells	Negatively regulates NLRP3-dependent inflammasome to suppress pyroptosis in endothelial cells	Wan et al. (2024)

Endotelyal disfonksiyon ve mikrosirkülasyon değişimi

SHOCK, Vol. 34, Supplement 1, pp. 27–33, 2010

› Expert Opin Ther Targets. 2021 Sep;25(9):733-748. doi: 10.1080/14728222.2021.1988928. Epub 2021 Oct 22.

Endothelial dysfunction: a therapeutic target in bacterial sepsis?

Jean-Louis Vincent [1], Can Ince [2], Peter Pickkers [3]

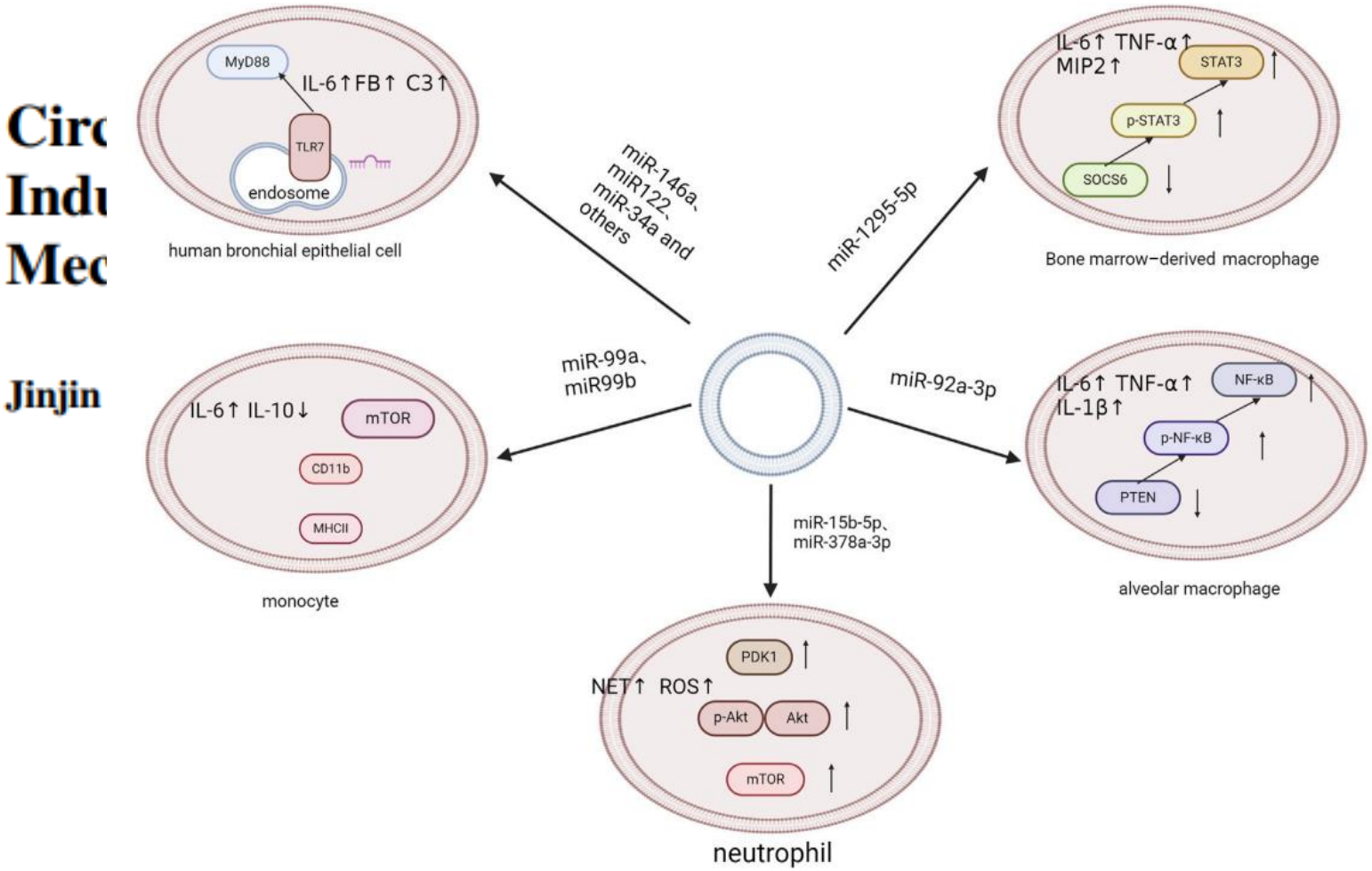
shock.

KEYWORDS—Microcirculation, severe sepsis, septic shock, intravital microscopy, sidestream dark-field imaging, orthogonal polarization spectral imaging

Endotelyal disfonksiyon ve mikrosirkülasyon değişimi

Pathological phenotype	miRNA	Regulation in sepsis	Sample source	Target cell	Potential functional mechanism	Ref.
Endothelial dysfunction and microcirculatory alterations	miR-15b-5p and miR-378a-3p	Up	Platelet	Neutrophil	Targeting PDK1 to modulate the Akt/mTOR pathway and then promote NET formation	Jiao et al. (2020)
	miR-1-3p	Up	Plasma	HUVECs	Targeting SERP1 inhibits cell proliferation, and increases monolayer endothelial cell permeability and membrane injury	Gao et al. (2021)
	miRNA-155 and miR-146a	Up	Broncho-alveolar lavage	Bronchial epithelial cells	Not described	Yuan et al. (2018)
	miR-223	up	Platelet	HCAECs	Downregulating ICAM1 expression	Szilágyi et al. (2021)

Multiple İnflamatuvar yolak aktivasyonu



EV-miRNAs Tedavide kullanımları
Mezenkimal kök hücre derive EV-miRNAs

Sample source	miRNA	Sample source	Target cell or organ	Related mechanism	Ref.
MSC	miR-223	MSC	Cardiomyocyte	Inhibit the expression of SEMA3A and STAT3, which reduces the inflammatory response and cell death	Wang et al. (2015)
	miR-146a	βMSCs	Macrophages	Promote M2 polarization through alterations in paracrine activity	Song et al. (2017)
	miR-21	βMSCs	Macrophages	Promote macrophage polarization to M2-like phenotype *in vivo* and *in vitro* by targeting *PDCD4*	Yao et al. (2021)
	miR-146b	human umbilical cord mesenchymal stem cell	Renal tubular cells	Regulate NF-κB activity by targeting *IRAK1*	Zhang et al. (2020a)
	miR-27b	MSC	Macrophages	Downregulate JMJD3 and inactivate the NF-κB signaling pathway	Sun et al. (2021)
	miR-17	MSC	Macrophages	Inhibit inflammation and apoptosis by targeting *BRD4/EZH2/TRAIL* axis	Su et al. (2021)
	miR-141	BMSC	Myocardial tissues	Alleviate sepsis-induced myocardial injury by targeting *PTEN* and activating b-catenin	Pei et al. (2021)
	miR-191	BMSC	Macrophages	Target the 3′-UTR of the DAPK1 mRNA and therefore suppress its translation	Liu et al. (2022b)
	miR-26a-5p	MSC	Murine hepatocytes	Inhibit anti-oxidant system by targeting MALAT-1	Cai et al. (2023)

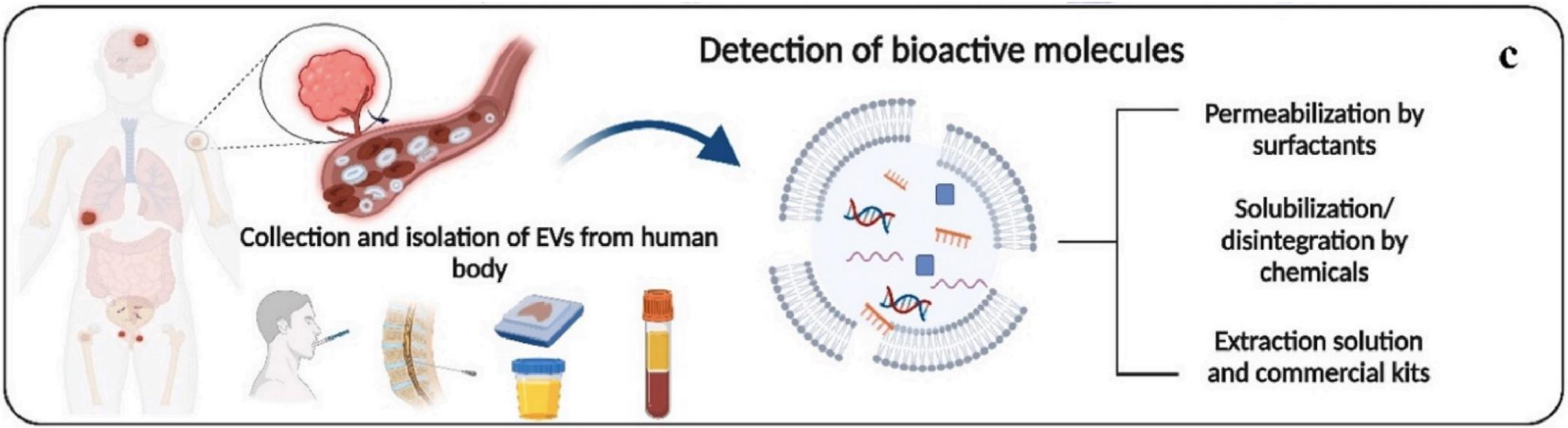
EV-miRNAs Tedavide kullanımları
Endotelyal progenitor hücre derive EV-miRNAs

Sample source	miRNA	Sample source	Target cell or organ	Related mechanism	Ref.
	miR-126-5p and 3p	EPC	Airway epithelial cells	Inhibit *PIK3R2* and *HMGB1* and increasing the levels of tight junction proteins	Zhou et al. (2019)
	miR-93-5p	EPC	HK2 cells	Silence of KDM6B activated H3K27me3 to inhibit TNF-α activation	He et al. (2020)
	miR-21-5p	EPC	Renal tissues	Alleviate the inflammatory and oxidative stress responses and reduce apoptosis in CLP rat by targeting *RUNX1*	Zhang et al. (2021)
	miR-382-3p	EPC	Murine lung, kidney and liver tissues	Inactivate IκBα/NFκB signaling pathway and alleviated the immune suppression by targeting BTRC	Liu et al. (2022a)

EV-miRNAs Tedavide kullanımları
Kandan derive EV-miRNAs

Sample source	miRNA	Sample source	Target cell or organ	Related mechanism	Ref.
Blood	miR-21	Serum	Mouse tubular epithelial cells	Suppress the activation NF-κB and notch signaling, reducing M1 macrophage polarization	Pan et al. (2019)
	miR-145	Blood	BEAS-2B cells	Partially suppresses *TGFBR2/Smad3* signaling	Cao et al. (2019)
	miR-126	Blood	Endothelial cells	Inhibit the mRNA of *VCAM-1* and suppress adhesion molecule expression	Harris et al. (2008), Zhang et al. (2020b)
	miR-142-5p	Serum	Lung tissues	Inhibit *PTEN* and activation of the PI3K/Akt signaling pathway	Zhu et al. (2022)

Tanıda EVs izolasyonu



SONUÇ

- Yeni nesil tanı testleri

-Prognostik belirteçlerin tanımlanması

-Tedavi yanıtının takip edilmesi

-Yeni tedavi hedeflerinin belirlenmesi

Application Area	Role of miRNA
Diagnosis	Early, specific detection of sepsis
Prognosis	Mortality risk prediction, severity scoring
Monitoring	Tracking response to antibiotics or supportive care
Therapeutics	Novel targets for immune modulation
Personalized Medicine	Patient-specific profiling and treatment planning